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Genetic polymorphisms possibly implicated in Diabetes Mellitus

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SUMMARY: Diabetes mellitus refers to a group of diseases that affect how the body uses blood sugar (glucose). Glucose is an important source of energy for the cells that make up the muscles and tissues. It's also the brain's main source of fuel. Many genetic polymorphisms are possibly implicated in Diabetes Mellitus. The main polymorphisms are Single-nucleotide polymorphism (-308G>A) in the TNF-α promoter, S477X polymorphism of LPL gene, A6244G polymorphism of IRS-1 gene, Polymorphisms in metallothionein-1and 2 genes, Polymorphisms in genes encoding adiponectin (ADIPOQ) and interleukin-6 (IL6), G Protein β3 Gene Variant, Endothelial Nitric Oxide Synthase Gene Polymorphisms, Estrogen receptor alpha gene and Renin-angiotensin aldosterone system gene polymorphisms.

INTRODUCTION

Diabetes Mellitus has become a major healthcare issue for the Western world over the years as it is shown in Figure 1 (Trapali, et al., 2022). The Centers for Disease Control and Prevention (CDC) has recently released the 2022 National Diabetes Statistics Report. This report estimates that more than 130 million adults are living with diabetes or prediabetes in the United States (Fig.1). Chronic diabetes conditions include type 1 diabetes and type 2 diabetes. Diabetes happens when blood sugar levels are higher than normal.

Diabetes Mellitus is characterized from decreased secretion or decreased action of

insulin (insulin reaction). 85-90% of Diabetic patients type 2 are obese, the usual age of onset is 40-60 years while risk factors can be genes/heredity, unhealthy lifestyle (poor diet, lack of exercise). Adipose tissue is a very active endocrine organ, secreting a number of hormones, such as adiponectin, leptin, resistin and visfatin, collectively with classical cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). All these adipocytokines play significant role in the regulation of energy metabolism, the metabolism of glucose and lipids, reproduction, cardiovascular function and immunity (Trapali, et al., 2022). Many genetic polymorphisms are possibly implicated in Diabetes Mellitus. The main polymorphisms are Single-nucleotide polymorphism (-308G>A) in the TNF-α promoter, S477X polymorphism of LPL gene, A6244G polymorphism of IRS-1 gene, Polymorphisms in metallothionein-1and 2 genes, Polymorphisms in genes encoding adiponectin (ADIPOQ) and interleukin-6 (IL6), G Protein β3 Gene Variant, Endothelial Nitric Oxide Synthase Gene Polymorphisms, Estrogen receptor alpha gene and Renin-angiotensin aldosterone system gene polymorphisms.

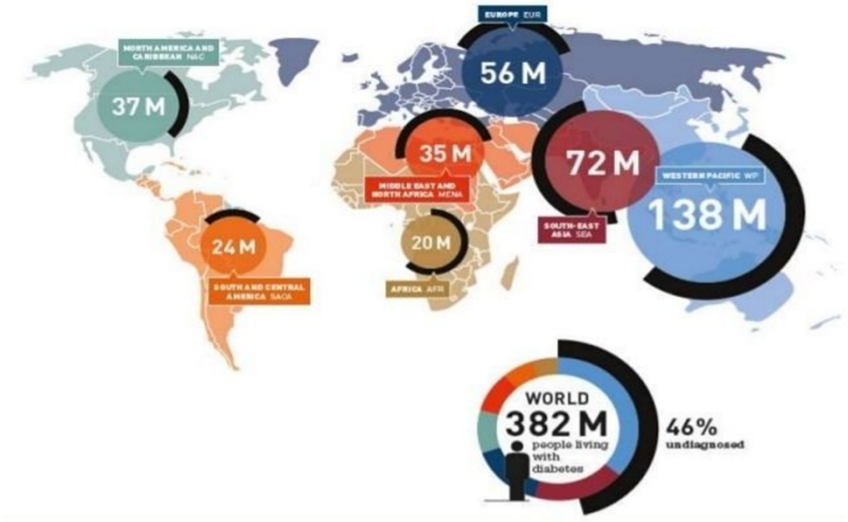

Figure 1: Diabetes epidemiology

1. Single-nucleotide polymorphism (-308G>A) in the TNF-α promoter

Tumor necrosis factor α (TNF-α) is a multifunctional cytokine that participates in many different pathways in mammalian homeostasis and pathophysiology. It can participate in opposite biological actions, which means complex regulation mechanisms. TNF-α was first identified as a cytotoxic agent that causes the lysis of certain cancer cells. The TNF-α gene is a member of the TNF-α superfamily (consisting of at least 20 different members). TNF-α plays a central role in inflammation, immune system development, apoptosis and lipid metabolism. It is also implicated in a number of pathological conditions including asthma, Crohn's disease, rheumatoid arthritis, neuropathic pain, obesity, type 2 diabetes, septic shock, autoimmunity and cancer. The multiple biological functions of TNF-α include cell proliferation and differentiation, tumorigenesis, apoptotic or necrotic cell death, immunoregulatory functions, lipid metabolism, thrombosis, and endothelial function. It promotes local or systemic inflammation (TNF-α is a potent pyrogen) and stimulates the acute phase response. Very high concentrations of TNF-α after infection can lead to septic shock (TNF-α is highly cytotoxic), while low levels induce cachexia and inflammation (Trapali, et al., 2022). There is a very concrete relationship between levels of TNF-α in adipose tissue and the scope of

hyperinsulinemia in human. TNF-α represses the insulin induced tyrosine kinase activity of insulin receptor (Hotamisligil , 1999). So, it mainly figurative an acute phase response to myocardial reduction of insulin receptor signaling through reducing auto-phosphorylation and tyrosine kinase activity. TNF-α controls expression of NF-κB which in turn induces expression of inflammatory and antiapoptotic gene network (Tian, et al., 2005). The -308 position of TNF-α promoter is a very important one for binding of nuclear proteins and alteration of its aspect. Polymorphism at -308 position in TNF-α affects binding of transcription factors resulting elevated expression of TNF-α (Ghazouani, et al., 1995).

Nucleotides change in the promoter region often cause vibration in expression, results in complications like dyslipidemia and atherosclerosis that ultimately exploit to coronary heart disease (CHD). There have been found significant ($P < 0.05$) relationship between TNF-α (308G>A) polymorphism and CHD in T2DM patients (Rezuan, et al., 2021), (Jamil, et al., 2015). A meta-analysis showed that TNF-α promoter (-308G>A) polymorphism has 1.5-fold intensified sense of affecting CHD in Caucasian (Zhang, et al., 2011). Another study (Sbarsi, et al., 2007) performed in Italian people stated that the incidence of TNF-α (-308G>A) polymorphism is significantly high in those people with diabetes. The same was found in Mexican population (Perez-Luque, et al., 2012) after examination the allelic frequencies of the TNF-α − 308G/A promoter gene in three groups: healthy subjects with and without family history of DM2 and in DM2 patients, and its relationship with insulin resistance, leptin and TNF-α levels. Finally, TNF-a 238G/A polymorphism may be a risk factor in the development and progression of prediabetes (Dutta, et al., 2013).

2. S477X polymorphism of LPL gene involved in essential hypertension (EHT) and type 2 diabetes mellitus (T2DM)

Lipoprotein lipase (LPL) is an extracellular enzyme on the vascular endothelial surface that degrades circulating triglycerides in the bloodstream. These triglycerides are embedded in very low-density lipoprotein (VLDL) and chylomicrons that travel through the bloodstream. The role of lipoprotein lipase is important in understanding the pathophysiology of familial dyslipidemias type one or hyperchylomicronemia and its clinical manifestations. Clinically, LPL plays an important role in the progression of atherosclerosis. LPL is a macrophage-derived component. Patients with advanced atherosclerosis were found to have increased LPL mass and activity in their plasma. LPL contributes to the formation of atherogenic lipoproteins. LPL acts on chylomicrons and VLDL to hydrolyze triglycerides. S477X polymorphism of LPL gene may regulate hypertension and it plays a key role in the transportation of serum lipoprotein and energy metabolism. The results of this study show that there was no significant difference found between S477X polymorphism and Malaysian hypertensive and type 2 diabetic subjects ($p>0.05$). (Vasudevan, et al., 2009)

3. A6244G polymorphism of IRS-1 gene involved in essential hypertension (EHT) and type 2 diabetes mellitus (T2DM)

Insulin is a hormone created by pancreas that controls the amount of glucose in your bloodstream at any given moment. It also helps store glucose in your liver, fat, and muscles. Finally, it regulates body's metabolism of carbohydrates, fats, and proteins. Biological actions of insulin are initiated when insulin binds to its cell surface receptor. Insulin receptor substrate-1 (IRS-1) is the first substrate of the insulin receptor in the insulin signaling pathway (Vasudevan, et al., 2009). Several polymorphisms have been described in this gene, among that a silent mutation in exon 8 of the insulin receptor gene at alanine. An A-to-G transition at nucleotide 6224 introducing a NsiI restriction site has been associated with arterial hypertension and blood pressure.

4. Polymorphisms in metallothionein-1and 2 genes

Metallothionein 1 is a metal transporter and antioxidative protein that maintains physiological element balance and prevent organ damage caused by an overload of metals. Many factors, such as heavy metals, antioxidants, alkylating agents, glucocorticoids, cytokines, and lipopolysaccharide, can trigger MT1 expression to produce a series of immunomodulatory effects. The frequency distributions of the G allele in SNP rs8052394 of MT1A gene is significantly associated with the incidence of type 2 diabetes.

For diabetic patients, serum superoxide dismutase action was notably lower in GG or GA carriers than those of AA carriers of rs8052394 SNP (Yang, et al., 2008) (Dai, et al., 2021).

5. Polymorphisms in genes encoding adiponectin (ADIPOQ) and interleukin-6 (IL6)

Adiponectin is a hormone and an adipokine protein that affects several metabolic processes and is mainly known for its insulin-sensitizing and anti-inflammatory effects. Adipose tissue (body fat) is mainly responsible for producing adiponectin. Interleukin 6 (IL-6) is a multi-functional cytokine that regulates immune responses, acute phase reactions and hematopoiesis and plays a central role in host defense mechanisms. The gene for IL-6 in humans has been located on chromosome 7. Its expression is readily induced by a variety of cytokines, lipopolysaccharide (LPS), and viral infections. Interleukin 1 beta (IL-1β) is a cytokine protein that in humans is encoded by the IL1B gene. ADIPOQ and IL6 variants were not directly related to obesity, leptin resistance or alterations in cardiometabolic markers. Individuals having ADIPOQ 45G allele (TG + GG genotype) had higher IL-6, IL-1β and TNFα levels than TT genotype carriers ($p < 0.05$). IL6 -174GG genotype was associated with increased IL-1β levels ($p = 0.033$). Type 2 diabetes, hypertension, dyslipidemia and increased values of waist circumference, body fat, leptin, fibrinogen, IL-1β and TNFα are related to obesity ($p < 0.05$) (De Oliveira, et al., 2015). Adiponectin gene polymorphism rs266729 is associated with CVD in T2DM patients. Carriers of the homozygous genotype (GG) have seven-fold risk of development of CVD, furthermore the risk in (CG) genotype carriers was two folds. Carriers of (rs266729) polymorphism of adiponectin gene are more predisposed to the progress of cardiovascular diseases and metabolic syndrome (Ismail, et al., 2016). The IL-1β (−511C/T) and IL-1RN (VNTR) polymorphisms are also correlated with increased risk of T2DM as well as related complications in North Indians (Achyut, et al., 2007).

6. G Protein β3 Gene Variant

Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-3 is a protein that in humans is encoded by the GNB3 gene. The GNB3 825T homozygous genotype has been related with rising body mass index (BMI) among different populations. GNB3 gene polymorphism causes important phenotypic changes in type 2 diabetes mellitus (Fernández-Real, et al., 2013).

7. Endothelial Nitric Oxide Synthase Gene Polymorphisms

Endothelial NOS (eNOS), also known as nitric oxide synthase 3 (NOS3) or constitutive NOS (cNOS), is an enzyme that in humans is encoded by the NOS3 gene located in the 7q35-7q36 region of chromosome 7. It has a protective function in the cardiovascular system, which is attributed to NO production. Regulation of the vascular tone is one of the best-known roles of NO in the cardiovascular system. Binding of transcription factors such as Sp1, Sp3, Ets-1, Elf-1, and YY1 to the NOS3 promoter and DNA methylation suggests an significant mechanism of transcriptional regulation.Endothelial nitric oxide gene polymorphisms, 894G/T, and 2479G/A could modify the plasma nitric oxide and homocysteine levels which may eventually rise the risk of deep vein thrombosis (Akhter, et al., 2022). The C allele for - 786T > C and the T allele for 894G > T have been found to be significantly more frequent in diabetics with nephropathy than in diabetics without nephropathy (Shoukry, et al., 2012).

8. Estrogen receptor alpha gene

Estrogen is a steroid hormone that effects many physiological processes, which include female reproduction, cardiovascular control, and bone purity. Estrogen exerts constructive systemic effects on lipoprotein and antioxidant metabolism. The estrogen receptor α (ERα) is a ligand-dependent transcription factor that regulates a large number of genes in many different target tissues and is important in the development and progression of breast cancer. ERα-mediated transcription is a complex process regulated at many different levels. It has been found difference in the frequency of C and G polymorphic allele between patients and control groups in PvuII and XbaI respectively in T2DM. Also, carriers of minor C and G alleles of PvuII and XbaI gene polymorphisms were associated with increased fasting blood glucose and disorder in lipid profile as there is an increase in total cholesterol, triglycerides and Low-density

lipoprotein (Eregat, et al., 2019) (Motawi , et al., 2015).

9. Renin-angiotensin aldosterone system gene polymorphisms

The renin-angiotensin-aldosterone system RAAS, is principally connected with blood pressure regulation by balancing blood volume, sodium reabsorption, potassium flow, water reabsorption, and vascular tone. Other described functions of the RAAS include inflammation, apoptosis, and fibrosis. Genetic modifications of angiotensin converting enzyme, angiotensinogen (AGT), angiotensin type 1 receptor, aldosterone synthase (CYP11B2), adducin, renin of RAAS have been performed in association with diabetic complexity.A6G (M235T) variant of AGT gene is significantly associated in hypertension with or without T2DM (Rodrıguez-Perez, et al., 2001).

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